REMARKS

Claims 33, 35, 53, 78, and 80-89 are pending in the application, claims 55 and 79 having been cancelled and new claims 86-89 added. The amendments to claims 80, 81, 83, and 84 are supported by, for example, page 35, line 28, of the specification. New claims 86 and 88 are supported by pending claim 53 and cancelled claim 55, and new claims 87 and 89 are supported by pending claim 78 and cancelled claim 79; these claims merely incorporate dependent claims into independent claims in order to make them allowable, as suggested by the Examiner (Office action, p. 5), or alternate between "consisting" and "comprising" language. No new matter has been added.

The invention is drawn to methods of testing candidate compounds for the ability to act as agonists of high affinity melatonin receptor ligands.

All of the claims were rejected or objected to on various grounds, discussed in detail below.

Claim Rejections – 35 USC § 112, first paragraph

Claims 80-85 are rejected in the Office action under 35 U.S.C. §112, first paragraph, as containing subject matter allegedly not described in the specification in such a way as reasonably to convey possession of the invention at the time of its filing.

Applicants have amended independent claims 80, 81, 83, and 84 (and, by extension, dependent claims 82 and 85) to recite "100 μg/ml denatured salmon sperm" instead of "100 mg/ml denatured salmon sperm". Applicants' March 22, 2002, amendment inadvertently recited the metric prefix "m" instead of "μ". This amendment adds no new matter.

Claims 33, 35, 53, and 78 are rejected in the Office action for lacking adequate written description under 35 U.S.C. §112, first paragraph. The Office action cites *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) as holding that "a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification" (Office action, p. 3). The Office action then states: "Thus, the only disclosure of a specific human melatonin receptor does not

have written description for the genus of human melatonin receptor whose sequences cannot be envisioned" (Office action, p. 3).

Applicants again traverse this ground for rejection. As previously pointed out, the case cited in the Office action, *Eli Lilly and Co.*, is inapposite to the pending claims because its holding concerns written description of cDNA claims, not method claims.

In *Eli Lilly and Co.*, the claims at issue were drawn to cDNA molecules - not, as in the present case, screening assays. The court held that a claim to a genus of cDNA molecules (such as all cDNAs encoding mammalian insulin) was not adequately supported by a description of a single species within the genus, and amounted to an attempt to claim a genus of compounds by function rather than structure. The holding thus applies to claims that cover cDNAs per se, as compositions of matter. The court did not indicate that the holding was meant to apply to all claims in which DNA or genes were mentioned anywhere in the claim. Indeed, method claims often use functional language to describe the various compositions utilized in the claimed method. Such language is rarely if ever challenged as failing to meet the written description requirement, so long as the language was present in the original application as filed. To illustrate, note that the claims of the present case employ the terms "candidate compound" and "mammalian cell" as reagents utilized in the claimed methods. Such terms are very typical for screening assay claims, and do not raise written description issues even though no description of the compound's or cell's actual structure is provided in the specification. While a composition claim drawn to a "candidate compound" or a "mammalian cell" itself would obviously require substantial further description in order to be patentable, method claims can and often do specify reagents with no additional written description of the reagents beyond general or functional language. There is certainly nothing in the *Eli Lilly and Co.* opinion to indicate that the court intended to change that widespread practice just because a reagent used in a claimed screening assay is a DNA molecule. Thus, there is no basis for trying to fit the present case under the holding in *Eli Lilly and Co.*.

Furthermore, applicants dispute that use of "substantially identical" "does not limit the structural difference with the recited SEQ ID NO:" (Office action, p. 3). In fact, applicants do provide a detailed definition of "substantially identical" amino acid sequence in the specification,

on page 5, lines 7-22, that specifically explains and limits the structure of the claimed amino acid sequences.

Applicants respectfully note that the Examiner has not provided any specific refutation of applicants' previous arguments against this ground for rejection. Rather, the Examiner has repeated almost verbatim his rejection from the advisory action (mailed December 10, 2001) and final Office action (mailed February 27, 2001). Applicants have thoroughly addressed and refuted this ground of rejection twice before, yet the Examiner still has not offered any rationale to explain why he believes applicants' reasoning to be flawed. It is the duty of an Examiner to provide a full explanation of a ground for rejection rather than an explanation that is stereotyped (MPEP 707.07(e)).

In light of the above, applicants respectfully request that this ground for rejection be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 33, 35, 53, and 78 are rejected in the Office action under 35 U.S.C. §112, second paragraph, as being indefinite with respect to either "high affinity melatonin receptor" or "substantially identical".

The Examiner considers the term "high affinity melatonin receptor", recited in claims 33 and 35, to be indefinite. The Examiner notes that the reference supplied by applicants to define the term "high affinity melatonin receptor" (Dubocovich *et al.*, *Molecular pharmacology and function of melatonin receptor subtypes*, pages 181-190 *In* Melatonin after four decades: an assessment of its potential, Edited by James Olcese, Kluwer Academic/Plenum Publishers, New York, 2000) was published subsequent to the filing date of the pending patent application. However, while this reference itself was published in 2000, it is a review article that includes data regarding the affinity of melatonin receptors derived from a reference published in 1988 (that is, Dubocovich, M.L., *Pharmacology and function of melatonin receptors*, FASEB Journal 2:2765-2773, 1988). Besides providing a discussion of the relative affinity for melatonin of high affinity and non-high affinity melatonin receptors, Dubocovich (1988) showed, at pages 2769-2770, that high affinity melatonin receptors can be characterized as having much greater affinity for melatonin than for the melatonin precursor N-acetylserotonin (also known as N-acetyl-5-

hydroxytryptamine), whereas non-high affinity melatonin receptors have equal affinity for melatonin and N-acetylserotonin. (Applicants have included a copy of this reference for the convenience of the Examiner; a copy of it was previously submitted as part of the information disclosure statement in the parent case.) Thus, it was known in 1988 that there are two classes of melatonin receptors (that is, high affinity and non-high affinity melatonin receptors) that can be distinguished biochemically as well as by relative affinity for melatonin. Based on these criteria, one of skill in the art could distinguish a high affinity melatonin receptor from a non-high affinity melatonin receptor.

The Examiner also considers "substantially identical", recited in claims 53 and 78 to be indefinite. However, the Examiner's attention is drawn to the detailed definition of a "substantially identical" amino acid sequence in the specification, on page 5, lines 7-22.

In light of the above, applicants respectfully request that this ground for rejection be withdrawn.

Claim Objections

Claims 55 and 79 are objected to as being dependent upon rejected base claims (Office action, p. 5). Accordingly, claims 55 and 79 have been cancelled and replaced with new claims 86 and 87, respectively. Applicants have also added new claims 88 and 89, which differ only from claims 86 and 87, respectively, by exchanging "comprising" with "consisting of" language, and vice versa. Applicants assume that the acceptability of employing "consisting of" language in claim 55 and "comprising" language in claim 79 also applies to new claims 89 and 88, respectively. These amendments add no new matter.

In light of these amendments, applicants respectfully request that these objections be withdrawn.

CONCLUSIONS

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a $400 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: October 22, 2002

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Version with markings to show changes made

In the claims:

Claim 80, 81, 83, and 84 have been amended as follows:

-- 80. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes to a probe having the sequence of the complement of SEQ ID NO:5 under the following conditions: hybridization in 50% formamide, 1 M sodium chloride, 1% SDS, 10% dextran sulfate, 100 [m]µg/ml denatured salmon sperm at 42 °C, and filters washed in 2x SSC, 1% SDS at 65 °C for 1 hour;

b) measuring intracellular cAMP concentration in said cell; and

c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

81. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes to a probe having the sequence of the complement of SEQ ID NO:5 under the following conditions: hybridization in 25% formamide, 1 M sodium chloride, 1% SDS, 10% dextran sulfate, 100 [m]µg/ml denatured salmon sperm at 42 °C, and filters washed in 2x SSC, 1% SDS at 55 °C for 1 hour;

b) measuring intracellular cAMP concentration in said cell; and

c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

83. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes to a probe having the sequence of the complement of SEQ ID NO:11 under the following conditions: hybridization in 50% formamide, 1 M sodium chloride, 1% SDS, 10% dextran sulfate, 100 [m]μg/ml denatured salmon sperm at 42 °C, and filters washed in 2x SSC, 1% SDS at 65 °C for 1 hour;

b) measuring intracellular cAMP concentration in said cell; and

c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand.

84. A method of testing a candidate compound for the ability to act as an agonist of a high affinity melatonin receptor ligand, said method comprising:

a) contacting said candidate compound with a cell comprising an expression vector encoding a high-affinity melatonin receptor protein, wherein the expression vector comprises a sequence that hybridizes to a probe having the sequence of the complement of SEQ ID NO:11 under the following conditions: hybridization in 25% formamide, 1 M sodium chloride, 1% SDS, 10% dextran sulfate, 100 [m]μg/ml denatured salmon sperm at 42 °C, and filters washed in 2x SSC, 1% SDS at 55 °C for 1 hour;

b) measuring intracellular cAMP concentration in said cell; and

c) where said contacting causes a decrease in intracellular cAMP concentration, identifying said candidate compound as an agonist of a high affinity melatonin receptor ligand. --